

PARTIAL TRISOMY 10Q (10Q25.1 → QTER) AND PARTIAL MONOSOMY 13Q (13Q34 → QTER) PRESENTING WITH FETAL PYELECTASIS: PRENATAL DIAGNOSIS AND ARRAY COMPARATIVE GENOMIC HYBRIDIZATION CHARACTERIZATION

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Distal trisomy 10q syndrome is a well-defined but rare syndrome characterized by a high and large forehead, a round and flat face, epicanthal folds, hypertelorism, fine eyebrows, antimongoloid slants, low-set ears, cleft palate, micrognathia, a flat nasal bridge, a short nose, a bow-shaped mouth, microcephaly, hypotonia, joint laxity, clinodactyly, scoliosis, a short neck, growth retardation, psychomotor disorders, and cardiac, ocular and renal abnormalities [1–6]. The critical region for distal trisomy 10q is proposed to be on 10q24 → qter [5].

The phenotype in patients with 13q deletion syndrome has been divided into three groups. Group 1 comprises deletions not extending into q32 and is associated with milder features and less developmental delay. Group 2 comprises distal deletions including at least a part of q32 and is associated with one or more major malformations related to the brain, eye, distal extremities, and gastrointestinal and genitourinary systems. Group 3 comprises more distal deletions involving q33–q34, and is associated with mental retardation in the absence of major malformations and growth retardation [7].

A concomitant occurrence of distal trisomy 10q and distal 13q deletion is unusual. We report array comparative genomic hybridization (aCGH) characterization of partial trisomy 10q (10q25.1 → qter) and partial monosomy 13q (13q34 → qter) in a fetus associated with fetal pyelectasis.

A 37-year-old woman, gravida 3, para 1, consulted the hospital at 20 gestational weeks for genetic counseling and confirmation of fetal aneuploidy. She previously had a healthy 3-year-old daughter and experienced one spontaneous abortion. During this pregnancy, she had undergone amniocentesis at 16 gestational weeks because of advanced maternal age. A derivative chromosome 13, or der(13), was found with a segment of distal 10q translocated to the terminal region of the long arm of chromosome 13. Level II ultrasound revealed a singleton with fetal biometry equivalent to 20 weeks and bilateral pyelectasis with the left pelvis measuring 0.61 × 0.80 cm and the right pelvis measuring 0.51 × 0.50 cm (Figure 1). At 21 gestational weeks, repeat amniocentesis revealed a der(13) in the fetus (Figure 2). The father was found to carry a balanced reciprocal translocation between distal 10q and distal 13q (Figure 3). The parents opted to terminate the pregnancy. A 324-g malformed male fetus was delivered with a high and large forehead, a flat face, hypertelorism, a flat nasal bridge, low-set ears, micrognathia, a short neck and clinodactyly (Figure 4). Bacterial artificial chromosome (BAC)-based aCGH of fetal DNA using CMDX BAC-based aCGH CA2500 chips (CMDX, Irvine,



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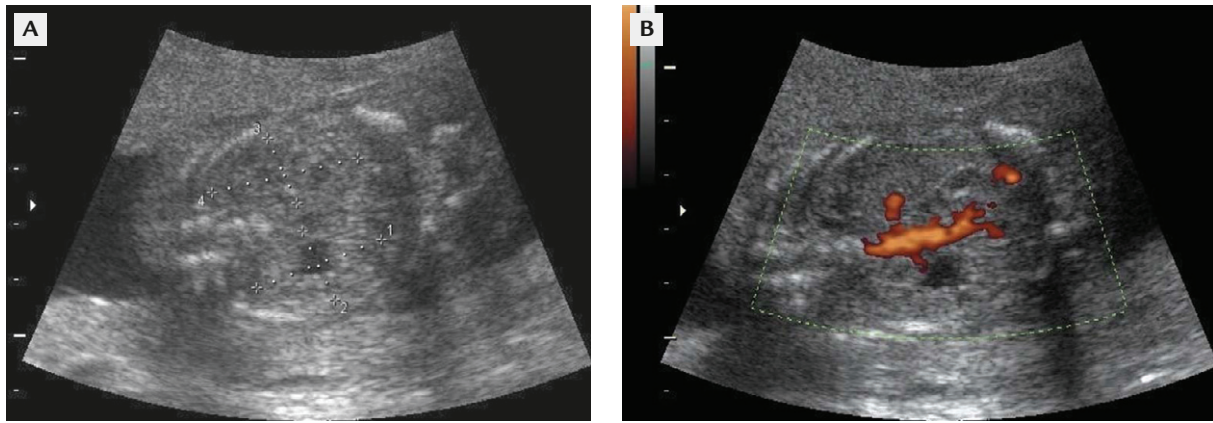


Figure 1. (A, B) Prenatal ultrasound at 20 gestational weeks shows pyelectasis with enlarged pelvises.

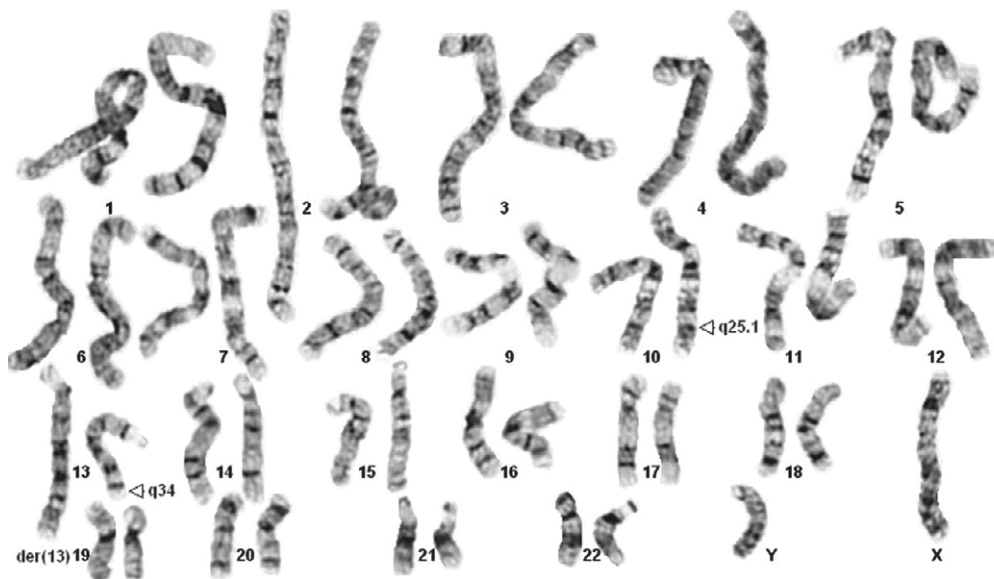


Figure 2. G-banded karyotype of the fetus shows a derivative chromosome 13, or der(13). The karyotype is 46,XY,der(13)t(10;13)(q25.1;q34)pat. The arrows indicate the breakpoints on normal chromosomes.



Figure 3. G-banded karyotype of the father shows a der(10) and a der(13). The karyotype is 46,XY,t(10;13)(q25.1;q34). The arrows indicate the breakpoints on normal chromosomes.



Figure 4. Anterior and lateral views of the craniofacial appearance of the proband.

CA, USA) demonstrated partial trisomy 10q and partial monosomy 13q [arr 10q25.1q26.3 (RP11-90J11→RP11-108K14)×3, 13q34q34 (RP11-192A14→RP11-450H16)×1] (Figure 5). Oligonucleotide-based aCGH using Oligo HD Scan (CMDX, Irvine, CA, USA) showed a 28.08-Mb duplication of distal 10q and a 1.12-Mb deletion of distal 13q [arr 10q25.1q26.3 (107,291,356-135,374,737)×3, 13q34q34 (112,930,168-114,142,980)×1] (Figure 6). The fetal karyotype was 46,XY,der(13)t(10;13)(q25.1;q34)pat. The paternal karyotype was 46,XY,t(10;13)(q25.1;q34).

The present case was associated with fetal pyelectasis and partial trisomy 10q (10q25.1→qter). Reported renal abnormalities associated with distal 10q trisomy syndrome include hypoplasia of the kidney and collecting system [1], absence of fetal lobulations and presence of cortical microcysts [8], unilateral renal and ureteral agenesis, contralateral renal dysplasia and a common ureterovaginal outlet [9], bilateral hydronephrosis [10,11], and bilateral pyelectasis [12–14]. An anteroposterior pelvic diameter > 5 mm defines fetal pyelectasis in the second trimester [15,16]. Recurrence of fetal pyelectasis within families has been described, and genetic and/or environmental factors are suspected [16,17]. Recurrence of fetal pyelectasis within a family with trisomy 10q (10q24→qter) has been reported indicating that renal collecting system anomalies can be an integral part of distal 10q trisomy syndrome [10–14]. The present case had a duplication encompassing 10q25.1→qter and did not involve the *NFκB2* gene (OMIM 164012) (104,144,219–104,152,271 bp, NCBI Build 36.3) at 10q24. Chen et al [14] previously suggested that a gene dosage increase of *NFκB2* may be responsible for uteropelvis junction obstruction leading to congenital hydronephrosis in patients with partial trisomy 10q (10q24→qter). *NFκB2* activation is associated with tissue inflammation, cellular proliferation and cellular differentiation [18]. Several studies

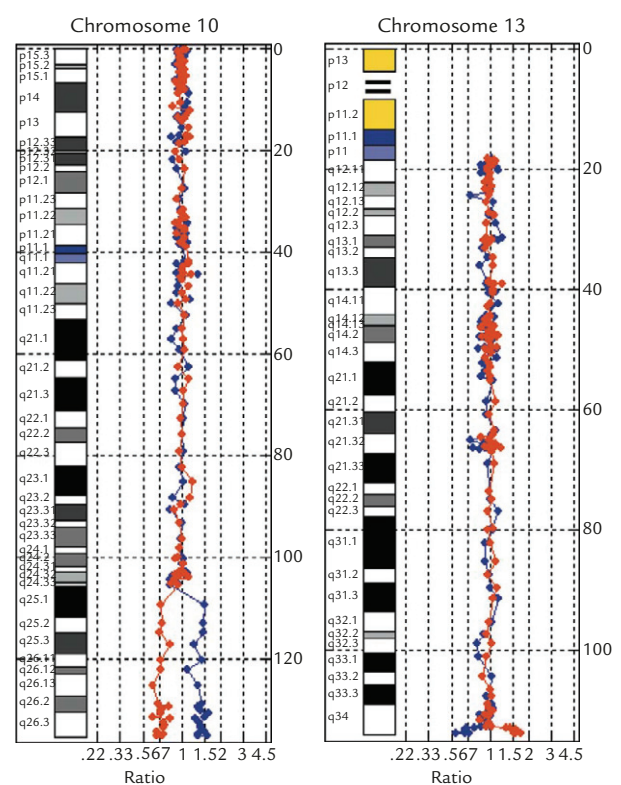
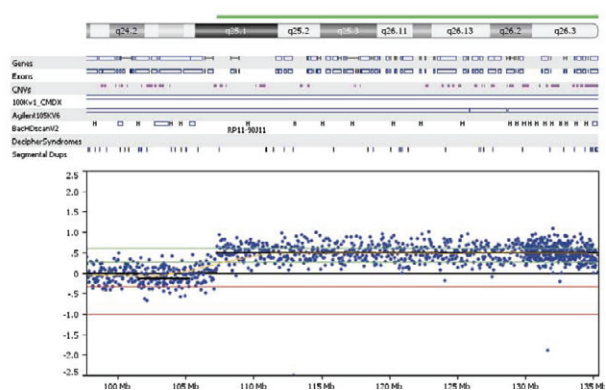
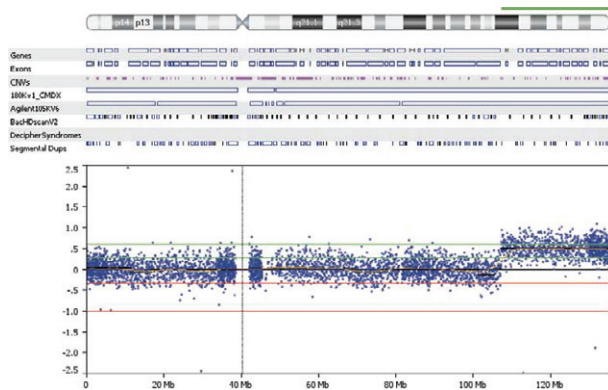


Figure 5. Bacterial artificial chromosome-based array comparative genomic hybridization shows partial trisomy 10q [arr 10q25.1q26.3 (RP11-90J11→RP11-108K14)×3] and partial monosomy 13q [arr 13q34q34 (RP11-192A14→RP11-450H16)×1].

have suggested that oxidative stress plays a role in interstitial inflammation and fibrosis, and activation of *NFκB* plays a role in hydronephrosis and obstructive nephropathy [19–22]. However, the present case provides evidence that distal trisomy 10q syndrome without the gene dosage increase of *NFκB2* can still be associated with fetal pyelectasis. It is likely that the chromosome segment distal to 10q24 contains genes associated with congenital hydronephrosis.

Chromosome 10



Chromosome 13

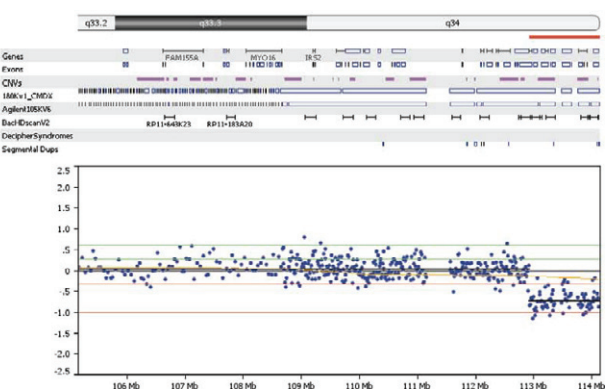
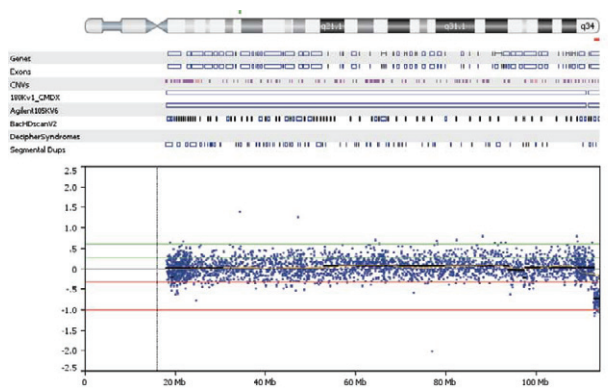


Figure 6. Oligonucleotide-based array comparative genomic hybridization shows (A) a 28.08-Mb duplication in 10q [10q25.1q26.3 (107,291,356-135,374,737)×3] and (B) a 1.21-Mb deletion of 13q [arr 13q34q34 (112,930,168-114,142,980)×1].

The present case belongs to group 3 of 13q deletion syndrome, which is thought to be associated with mental retardation in the absence of major malformations and growth retardation [7]. We previously reported a fetus with partial monosomy 13q (13q33.3→qter) associated with Dandy-Walker malformation and microcephaly [23], and a fetus with partial monosomy 13q (13q21.32→qter) associated with anencephaly [24]. The present case had partial monosomy 13q (13q34→qter) but manifested no major brain malformations. Kirchhoff et al [25] refined the smallest deletion linked to short stature (13q31.3), microcephaly (13q33.3-q34), cortical development malformations (13q33.1-qter), Dandy-Walker malformation (13q32.2-q33.1), corpus callosum agenesis (13q32.2-q33.1), meningocele/encephalocele (13q31.3-qter), Dandy-Walker malformation, corpus callosum and neural tube defects taken together (13q32.3-q33.1), anophthalmia/microphthalmia (13q31.3-qter), cleft lip/palate (13q31.3-q33.1), lung hypoplasia (13q31.3-q33.1) and thumb aplasia/hypoplasia (13q31.3-q33.1 and 13q33.3-q34). The present case manifested no microcephaly and did not involve the *ARHGEF7* gene (OMIM 605477) (110,565,783–110,756,079 bp) at 13q34. Walczak-Sztulpa et al [26] suggested that haploinsufficiency of the *ARHGEF7* gene

in patients with chromosomal deletions in 13q33-q34 is responsible for mental retardation and microcephaly. *ARHGEF7* maps to 13q34 and encodes Rho guanine nucleotide exchange factor 7. Mutations in other Rho guanine nucleotide exchange factors such as *ARHGEF6* and *ARHGEF9* have previously been associated with X-linked mental retardation [27,28].

In conclusion, prenatal sonographic detection of fetal pyelectasis should alert clinicians to the presence of chromosomal abnormalities and prompt cytogenetic investigation, which may lead to the identification of an unexpected parental translocation involving chromosomal segments associated with congenital hydronephrosis. The information acquired through perinatal studies is helpful for both genetic counseling and investigation in subsequent pregnancies.

Acknowledgments

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